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The expression and clinical significance of B7-H3 and miR-145 in lung cancer patients with malignant pleural effusion

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Abstract. – OBJECTIVE: To investigate the expression and clinical significance of costimulatory molecule B7-H3 and microRNA-145 (miR-145) in lung cancer patients with malignant pleural effusion.

PATIENTS AND METHODS: A total of 100 cases of patients with lung cancer who admitted to our hospital for treatment from March 2017 to September 2018 were selected. Forty-nine cases of patients diagnosed with malignant pleural effusion were included in the study group, and 51 cases with benign pleural effusion in the control group. The content of B7-H3 in pleural effusion of the two groups was detected by enzyme-linked immunosorbent assay (ELISA), and the expression of miR-145 in pleural effusion of the two groups was analyzed by Real-time quantitative PCR (qRT-PCR). The relationships between the expressions of B7-H3 and miR-145 and the clinicopathological characteristics were analyzed. The diagnostic value of B7-H3 and miR-145 in lung cancer was analyzed.

RESULTS: The expression level of B7-H3 in the study group was significantly higher than that in the control group ($p<0.050$), while the expression level of miR-145 was significantly lower than that in the control group ($p<0.050$). The expression levels of B7-H3 and miR-145 in the study group were correlated with lymph node metastasis, differentiation degree of lung cancer and TNM stage ($p<0.001$). The sensitivity and specificity of miR-145 in single diagnosis of lung cancer were 64.71% and 79.59%, respectively. The sensitivity and specificity of B7-H3 in single diagnosis of lung cancer were 80.39% and 61.22%, respectively.

CONCLUSIONS: B7-H3 and miR-145 are abnormally expressed in lung cancer, and are closely related to the lymphatic metastasis, differentiation degree and TNM stage of lung cancer. They may be potential markers for the diagnosis of malignant pleural effusion in lung cancer in the future.

Key Words:
Lung cancer, Malignant pleural effusion, B7-H3, MiR-145, Clinical pathology, Diagnostic value.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide[1]. According to statistics, 470,000 cases of lung cancer occurred in China in 2012[2], and the death rate of advanced lung cancer in South Korea reached 49.5% in 2013[3]. According to GLOBOCAN statistics in 2018, lung cancer is the most commonly diagnosed cancer, accounting for 11.6% of all cancer cases and 18.4% of all cancer deaths, which is the main cause of cancer deaths of males[4]. In the past two decades, non-small cell lung cancer accounts for 80% to 90% of lung cancer[5]. Malignant pleural effusion is a complication of many cancers, the most common of which is lung cancer[6]. About two-thirds of malignant pleural effusion are secondary to lung cancer, breast cancer and lymphoma[7]. While pleural effusion is closely related to non-small cell lung cancer. During early diagnosis, about 15% of cancer patients were diagnosed with malignant pleural effusion[8], which is usually accompanied by severe dyspnea[9,10]. There are still no effective treatments for malignant pleural effusion.

The field of immunotherapy is an expanding field of cancer biology research. Costimulatory molecule B7-H3 is a member of the B7 immunoregulation transmembrane glycoprotein family expressed by T cells[11], which has dual functions as a co-stimulator and co-inhibitor that can regulate mediated T-cell immune response[12]. According to relevant data, B7-H3 has been found to be expressed in gastric cancer[13], ovarian cancer[14], breast cancer[15] and other tumor cells. There are also relevant reports indicating that abnormal expression of B7-H3 may lead to carcinogenic effect through various mechanisms and it is an indicator of poor prognosis of cancer patients[16]. Therefore, it is of great significance to study the therapeutic effect of B7-H3 in lung cancer.

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MiRNA is a kind of non-coding RNA (about 22 nucleotides) that directly inhibit translation and/or mRNA destabilization through mRNA cleavage, playing an important role in post-transcriptional regulation of protein-coding genes[17]. As a tumor suppressor or cancer gene involved in cancer, miRNA is also a potential cancer biomarker[18]. It has been shown that micro RNA (miRNA) plays an important role in the progression of non-small cell lung cancer (NSCLC)[19]. Sachdeva et al[20] found that microRNA-145 (miR-145) is a tumor suppressor which not only inhibits tumor growth, but also inhibits cell invasion and metastasis. The low expression of miR-145 plays a significant role in the overexpression of the co-inhibitory molecule B7-H3 in colorectal cancer[21]. However, the roles of miR-145 and H7-B3 in malignant pleural effusion of lung cancer patients remain unclear.

Therefore, the expressions of B7-H3 and miR-145 in malignant pleural effusion of lung cancer patients were detected in this research, so as to investigate the clinical significance and diagnostic value of B7-H3 and miR-145 in malignant pleural effusion of lung cancer.

Patients and Methods

General Data of Patients

A total of 100 cases of patients with lung cancer admitted to our hospital from March 2017 to September 2018 were selected. Pleural effusion of all the study subjects was collected in our hospital and sent to the department of pathology for examination. Among them, a total of 49 patients diagnosed with malignant pleural effusion were included in the study group, including 31 males and 18 females, 37-75 years old, with an average age of 56.13±6.25 years old. Another 51 patients with benign pleural effusion were included in the control group, including 33 males and 18 females, 35-74 years old, with an average age of 54.82±6.81 years old. This study was conducted according to the Declaration of Helsinki by the World Medical Association. This invesitgation has been approved by the Ethics Committee of our hospital, and all the subjects have signed the informed consent. The cytology in pleural liquid was not observed in this study.

Inclusion and exclusion criteria: the inclusion criteria were as follows: patients consistent with clinical manifestations of lung cancer[22], patients diagnosed by biopsy in pathology department of our hospital, patients with normal coagulation function, patients diagnosed as malignant pleural effusion through pleural cytology combined with pleural biopsy; patients with benign pleural effusion without malignant tumor cells; patients received surgical treatment in our hospital after diagnosis, patients with complete case data, patients agreed to cooperate with the medical staff of our hospital without other serious organ diseases affecting this study. Patients or their immediate families signed the informed consent. Exclusion criteria were as follows: patients died during treatment, patients with damage to vital organs, patients with other tumors, patients with other cardiovascular and cerebrovascular diseases, patients with physical disability, pregnancy, or other autoimmune diseases, patients with other chronic diseases, patients who transferred to other hospitals, patients with contraindications to surgery, patients with mental disorders and language dysfunction as well as diseases affecting the results of this study.

Methods

All the patients underwent routine pleural puncture before treatment within 24 hours after admission. Pleural effusion (50 mL) was retained and centrifuged for 10 min (400 xg) after heparin anticoagulation. After that, the supernatant was absorbed and stored in the freezer at -80°C for measurement. All specimens were registered with the patient's name, age, hospitalization number and other basic information. The content of B7-H3 was detected by enzyme-linked immunosorbent assay (ELISA). The detection kit of B7-H3 was purchased from Thermo Fisher Scientific (88-50370-22, Waltham, MA, USA). The quantitative real-time fluorescence PCR (qRT-PCR) was used to measure miR-145, and the detection kit was purchased from Shanghai kemin biotechnology Co., Ltd., with the item number of (DXT-ST600733, Shanghai, China). The operation steps were carried out in strict accordance with the instruction. The primer sequences were shown in Table I.

Table I. Primer sequences.

	F	R
miR-145	5'-GTCCAGTTTTCCCAGGAAT-3'	5'-TGGTGTCGTGGAGTCG-3'
U6	5'-GCTTCGGCAGCACATATACTAAAT-3'	5'-CGCTTCACGAATTTGCGTGTCAT-3'

qRT-PCR Detection Assay

The total RNA of collected serum and hydrothorax of patients was extracted with EasyPure miRNA Kit reagent (purchased from TransGen Biotech Co., Ltd., Beijing, China, item number: ER101-01), and the procedures were in strict accordance with the manual. Uv spectrophotometer was used to detect the concentration and purity of the extracted RNA. The OD value of total RNA solution: A260/A280 ranged from 1.8 to 2.1. If the standard was not reached, it would be extracted again. RNA integrity was detected by 1% denatured agarose gel electrophoresis. By the miRNA reverse transcription kit (TransScript II Green Two-Step qRT-PCR SuperMix, TransScript Green miRNA Two-Step qRT-PCR SuperMix, TransGen Biotech Co., Ltd., Beijing, China, AQ301-01, AQ202-01) manual, cDNA was synthesized under the reaction system of configuration and reverse transcription of total RNA (stored at -20°C for stand-by). Real-time qPCR ABI StepOne Plus was used for determination. The reaction system was configured in accordance with the instructions. The reaction system was 12.33 uL in total and added to 20 uL with DEPC water. The reaction conditions were 95°C for 5 min, 95°C for 45 s, and 60°C for 60 s. A total of 45 cycles were performed at 72°C for 45 s. U6 was used as the internal parameter of the reaction. The experiment was repeated 3 times, and the results were analyzed by 2-ΔCt method.

Observational Indexes

The expression levels of B7-H3 and miR-145 in the two groups. The relationship between the concentration of B7-H3 and miR-145 and clinicopathology in the study group. The diagnostic value of B7-H3 and miR-145 in lung cancer.

Statistical Analysis

SPSS 24.0 statistical software (Beijing strong-vinda information technology Co., Ltd., China) was used for statistical calculation of all experimental results. GraphPad Prism 7 software was used for image rendering. Enumeration data were expressed by percentage (%). Comparison between the two groups was qualified by chi-square test. All measurement data were expressed in the form of (mean ± standard deviation). The t-test was used for comparison between groups. The ROC curve was used to evaluate the diagnostic efficacy and calculate the sensitivity and specificity. $p<0.05$ was considered statistically significant.

Results

Comparison of the Expression Levels of B7-H3 and MiR-145 in the two Groups

The relative expression level of miR-145 in the pleural effusion of the study group was 2.16 ±0.51, which was lower than that in the control group (3.07±0.50) ($p<0.050$). More details were shown in Figure 1A. The concentration of B7-H3 in pleural effusion of the study group was (64.32±14.18)

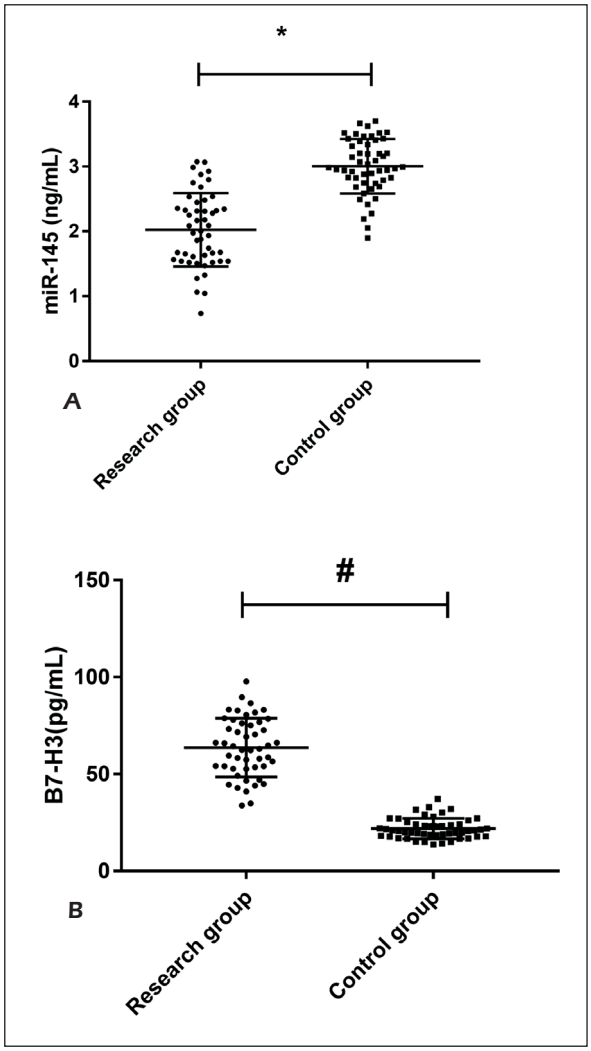

Figure 1. Comparison of the expression levels of B7-H3 and miR-145 in the two groups. **A**, Comparison of miR-145 expression levels between the two groups: the expression level in the control group was higher than that in the study group, with statistically significant differences ($p<0.05$). *means the expression levels of miR-145 between the two groups were compared. **B**, Comparison of expression levels of B7-H3 between the two groups: the expression level in the control group was lower than that in the study group, with statistically significant differences ($p<0.05$). #means the expression levels of B7-H3 between the two groups were compared.

pg/mL, which was significantly higher than that in the control group (21.63±5.17) pg/mL (p<0.050). More details were shown in Figure 1B.

The Relationship Between Concentration of B7-H3 and miR-145 and Clinicopathology in the Study Group

There were no significant differences in age, gender, disease course and other categories in the study group (p>0.050), and there were differences (p<0.050) in smoking, lymph node metastasis, TNM stage and differentiation degree classification (p<0.050). More details were shown in Table II and Table III.

The Diagnostic Value of B7-H3 and MiR-145 on Malignant Pleural Effusion Of Lung Cancer

When the cut-off value was 2.684, the sensitivity and specificity of miR-145 in single diagnosis of lung cancer were 64.71% and 79.59%, respectively. When the cut-off value was 32.17 (pg/mL), the sensitivity and specificity of B7-H3 in single diagnosis of lung cancer were 80.39% and 61.22%, respectively. More details were shown in Table IV, Figure 2A and Figure 2B.

Discussion

Lung cancer is the leading cause of cancer death among men and women in the United States, the leading cause of cancer death among men, and the second leading cause of cancer death among women globally[23]. There are two main subtypes of lung cancer: small cell lung cancer and non-small cell lung cancer, which account for 15% and 85% of all lung cancers respectively[24]. The pleural cavity of 1 million cancer patients is affected by malignant pleural effusion every year[25]. Malignant pleural effusion is manifested as intrapleural effusion result from vascular leakage, which is associated with fulminant inflammation and neovascularization[26]. Malignant pleural effusion is usually the result of the spread of metastatic cancer[27], and it is a common complication in advanced malignancies[28]. Malignant pleural effusion affects more than 750,000 people in Europe and the United States every year[29].

As an endogenous non-protein coding RNA molecule, expression and changes of miRNA have been proved to be directly involved in the occurrence and progression of tumors by increasing studies[30]. Most miRNAs are highly conserved, with specific tissue

Table II. The correlation between miR-145 and different clinical pathological features of lung cancer.

	N (49)	miR-145	F	p
Age (years old)			0.129	0.898
>55	28	2.17±0.55		
≤55	21	2.15±0.52		
Gender			0.196	0.846
Male	31	2.17±0.51		
Female	18	2.14±0.53		
Disease course (week)			0.132	0.896
>5	29	2.17±0.53		
≤5	20	2.15±0.51		
Smoking				
with	39	2.16±0.50	0.112	0.911
without	10	2.14±0.52		
Tumor size (cm)			0.132	0.896
>3	26	2.17±0.52		
≤3	23	2.15±0.54		
Lymph node metastasis			5.120	<0.001
with	27	2.16±0.51		
without	22	2.93±0.54		
TNM			5.842	<0.001
I-II	32	2.15±0.50		
III-IV	17	3.05±0.52		
Grade of Differentiation			6.567	<0.001
Poorly differentiated	26	2.18±0.49		
Highly differentiated	23	3.11±0.50		

Table III. The correlation between B7-H3 and different clinical pathological features of lung cancer.

	N (49)	B7-H3 (pg/mL)	F	*p*
Age (years old)			0.327	0.745
>55	28	6487±13.23		
≤55	21	63.58±14.21		
Gender			0.771	0.445
Male	31	65.47±13.64		
Female	18	62.34±13.81		
Disease course (week)			0.285	0.777
>5	29	64.76±12.78		
≤5	20	63.68±13.41		
Smoking			0.186	0.853
with	39	64.58±14.07		
without	10	63.65±14.12		
Tumor size (cm)			0.512	0.611
>3	26	65.32±14.87		
≤3	23	63.18±14.31		
Lymph node metastasis			11.910	<0.001
with	27	61.95±14.73		
without	22	22.58±5.27		
TNM			12.150	<0.001
I-II	32	21.43±4.83		
III-IV	17	63.18±13.67		
Grade of Differentiation			15.650	<0.001
Poorly differentiated	26	62.87±13.93		
Highly differentiated	23	20.76±5.62		

cell and other characteristics, having strong regulatory ability to cell proliferation and apoptosis[31]. MiR-145 is a tumor suppressor that is significantly downregulated in many cancers, which contributes to the growth of tumor cells[32].

B7-H3 is part of the B7 superfamily of immune checkpoint molecules; B7-H3 is closely related to cancer progression. In addition to immune escape, it also controls cancer progression in terms of cell invasion and migration, angiogenesis, and epigenetic gene regulation[33].

At present, the early diagnosis of lung cancer mainly relies on serum tumor markers such as CEA, CA199, etc. Although the response to the tumor is extremely significant, traditional markers also have abnormal performance for some inflammatory injuries, and have low specificity. Therefore, finding a new blood marker has extremely important clinical significance for the early screening of tumor diseases in the future. In this study, the expression levels of miR-145 and B7-H3 in malignant pleural effusion and benign pleural effusion of lung cancer patients were detected, initially revealing the future application of miR-145 and B7-H3 in lung cancer. After a more in-depth and comprehensive analysis, miR-145 and B7-H3 can be used as excellent indicators for the diagnosis, rehabilitation and prognosis of lung cancer

The results of this study showed that the relative expression level of miR-145 in the pleural effusion of lung cancer patients was significantly lower than that of the corresponding benign

Table IV. Clinical value of miR-145 and B7-H3 on malignant pleural effusion of lung cancer.

	miR-145	B7-H3
AUC	0.771	0.769
Std. Error	0.046	0.046
95% CI	0.681-0.861	0.678-0.859
p	<0.001	<0.001
Cut-off	2.684	32.17
Sensitivity [n (%)]	64.71%	80.39%
Specificity (%)	79.59%	61.22%

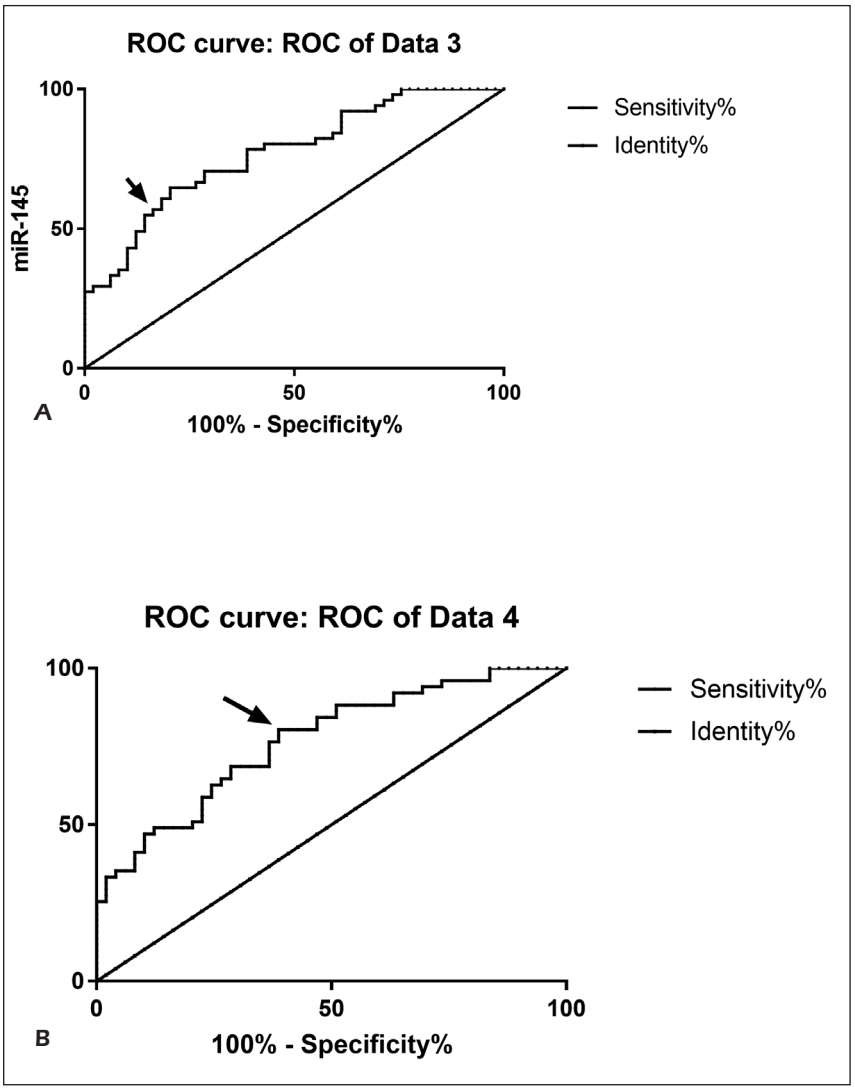

Figure 2. The diagnostic value of B7-H3 and miR-145 on lung cancer. **A**, ROC curve analysis of miR-145 expression: when the cut-off value was 2.684, the sensitivity and specificity of miR-145 in single diagnosis of lung cancer were 64.71% and 79.59%, respectively. $p<0.001$. **B**, ROC curve analysis of B7-H3 expression: when the cut-off value was 32.17 (pg/mL), the sensitivity and specificity of B7-H3 in single diagnosis of lung cancer were 80.39% and 61.22%, respectively. $p<0.001$.

pleural effusion ($p<0.05$), which was consistent with the research results of Kim et al[34] on miR-145 in ovarian cancer. The relative level of B7-H3 expression in pleural effusion of lung cancer patients was significantly higher than that in the corresponding pleural effusion ($p<0.05$), which was consistent with the results of Picarda et al[35] study on the high expression of B7-H3 in cancer. The relationships between miR-145 and B7-H3 and clinicopathology were analyzed, the result showed that the expressions of miR-145 and B7-H3 might be related to TNM stage, differentiation degree and lymph node metastasis of lung cancer. Xia et al[36] suggested in their study that the expression level of miR-145 could be a new prognostic marker for lung cancer, indicating that miR-145 might be related to tumor staging, lymph node metastasis and differentiation of lung cancer. In the study of Zhang et al[37], it was suggested that higher level of B7-H3 was associated with higher tumor stage, tumor size, lymph node metastasis and distant metastasis. By plotting ROC curves for miR-145 and B7-H3, it was found that the AUC of miR-145 was 0.771 (95% CI: 0.681-0.861), while the AUC of B7-H3 was 0.769 (95% CI: 0.678-0.859). It indicated that miR-145 and B7-H3 had great diagnostic value in the diagnosis of lung cancer. Wang et al[38] also suggested that miR-145 might be a biomarker of non-small cell lung cancer. In the study of Zhang et al[39], it was also suggested that B7-H3 was a valuable biomarker for non-small cell lung cancer.

However, there are still some shortcomings in this study. Due to limited experimental conditions, the sample of selected subjects is too small, and the expressions of miR-145 and B7-H3 may

be different in different age groups. In addition, due to the low 5-year survival rate of lung cancer patients, we failed to set up a follow-up survey in this study to observe the prognosis and survival of patients, so there are certain limitations. In the future, we will carry out the prognosis of such diseases according to the actual situation, deeply analyze the influencing factors of patients' quality of life, and further verify the results of this investigation.

Conclusions

To sum up, B7-H3 and miR-145 were both abnormally expressed in lung cancer, and are closely related to the lymphatic metastasis, differentiation degree, and TNM stage of lung cancer. They may be potential markers for the diagnosis of malignant pleural effusion in lung cancer in the future.

Conflict of Interests

The authors declare that there is no conflict of interest.

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